66. The compound of claim 46, wherein R_3 is -C(O)-CH_2-Z-G, and G is C-attached heteroaryl or a quaternary ammonium salt of a nitrogen containing heteroaryl group.

67. The compound of claim 46, wherein R_3 is -C(O)-CH_2-Z-G, and G is optionally substituted aryl or a quaternary ammonium salt of an amino substituted aryl group.--

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 25-27, 46, 55, 57-59 and 61-67 are pending in the application, with 27, 46 and 58 being the independent claims. Claims 35-43, 47-53, 56 and 60 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to file a divisional application to canceled subject matter. Claims 62-67 are sought to be added. New claims 62-67 are each directed to a subgenus of compounds from the genus of compounds of claim 46. Support for new claims 62-67 can be found, *inter alia*, at page 14, line 7, through page 17, line 8, page 23, line 9, through page 25, line 3, and in claim 1, of the application as filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Allowable Subject Matter

Applicants note with appreciation the Examiner's opinion that claims 27 and 59 contain allowable subject matter. Specifically, the Examiner stated that "[c]laims 27 and 59 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims." (Office Action, page 5, paragraph number 9). In the previous Amendment and Reply, filed March 23, 2000, claim 27 was amended to be independent. In this Amendment and Reply, claim 27 has been amended to further conform to U.S. claim style for an independent claim. Claim 59 is dependent upon claim 27. Applicants respectfully submit that claims 27 and 59 are fully in condition for allowance.

Claim Objection

The Examiner has objected to claim 25 under 37 CFR § 1.75(c) as being improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, the Examiner states that "[c]laim 25 which is dependent on claim 46 recites R_3 "-C(O)-CH_2-O-Y'-Z-G". Claim 46 does not include the group "-C(O)-CH_2-O-Y'-Z-G" instead it recites "-C(O)-CH_2-Y'-Z-G". It is suggested that "-C(O)-CH_2-O-Y'-Z-G" be amended to read "-C(O)-CH_2-Y'-Z-G"." (Office Action, paragraph 3).

Applicants have amended claim 25 according to the Examiner's helpful suggestion. Applicants respectfully submit that the Examiner's objection has been accommodated and should be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 25, 26, 46, 55, 57, 58 and 61 under 35 U.S.C. § 103(a) as being obvious in view of U.S. Patent No. 3,969,345 (Phillipps *et al.).* (Office Action, paragraph 8, lines 1-2). Specifically the Examiner is of the opinion that "Phillips et al. teach a generic group of 3α-oxygenated pregnane-21-ether derivatives having useful anesthetic activity (see entire article, especially col. 3, lines 38-66). The reference teaches compounds such as 21-p-aminophenoxy-3α-hydroxy-5α-pregnane-11,20-dione (col. 16, example 6) and 21-benzyloxy-3α-hydroxy-5α-pregnane-11,20-dione (col. 21, example 19)." (Office Action, paragraph 8, lines 3-7). The Examiner further states that "[t]he instant claims differ from the reference by reciting compounds wherein 3β-substituent is an alkyl instead of a hydrogen atom. However, hydrogen and methyl are considered obvious variant in the steroid art and, thus, the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results." (Office Action, paragraph 8, lines 8-12). Applicants respectfully traverse this rejection.

A. 21-p-aminophenoxy-3α-hydroxy-5α-pregnane-11,20-dione

Solely in the interest of advancing the prosecution of this application, claim 46 has been amended so that, when the 21-substituent is -O-E (including optionally substituted phenoxy), the 3β-substituent is not hydrogen or alkyl. Thus, the compounds of independent claim 46 and dependent claims 25, 26, 55 and 57 are not alkylene homologs of the compounds disclosed by the prior art, for example 21-*p*-aminophenoxy-3α-hydroxy-5α-pregnan-11,20-dione; and the

rejection is rendered moot.

Claim 58 has been amended so that, when the 21-position is substituted phenoxy (-O-(4-nitrophenyl) or -O-(4-dimethylaminophenyl)), the 3β-position is not hydrogen or alkyl. Thus, the compounds of independent claim 58 and dependent claim 61 are not alkylene homologs of the compounds disclosed by the prior art, for example 21-*p*-aminophenoxy-3α-hydroxy-5α-pregnane-11,20-dione; and the rejection is rendered moot.

Applicants respectfully submit that the Examiner's stated grounds for rejection has been overcome and should be withdrawn.

B. 21-benzyloxy-3α-hydroxy-5α-pregnane-11,20-dione

Solely in the interest of advancing the prosecution of this application, claim 46 has been amended so that when the 21-substituent is -Y'-Z-G (including benzyloxy), the 3β-substituent is not hydrogen or alkyl. Thus, independent claim 46 and dependent claims 25, 26, 55 and 57 are not obvious in view of the compounds disclosed by the prior art, for example 21-benzyloxy-3α-hydroxy-5α-pregnane-11,20-dione.

Claim 58 is directed to compounds in which the 21-position is -S-(4-fluorophenyl), -O-(6-quinolinyl), $-SO_2$-(4-fluorophenyl), $-SO_2$-(4-pyrrolidinophenyl), $-CH_2$-(4-pyridyl), -O-(4-nitrophenyl), -O-(4-dimethylaminophenyl), -SO-(4-nitrophenyl) and $-SO_2$-(4-nitrophenyl). None of these substituents are obvious in view of a benzoyloxy substituent. Thus, the compounds of independent claim 58 and dependent claim 61 are not adjacent homologs of the compounds disclosed by the prior art, for example 21-benzyloxy-3α-hydroxy-5α-pregnane-11,20-dione; and the rejection is rendered moot.

Applicants respectfully submit that the Examiner's stated grounds for rejection has been overcome and should be withdrawn.

C. Additional Argument

The Examiner is also of the opinion that "the reference teaches further substitution such as substitution of an alkyl or an aralkyl group in the 2-position and, thus, positional isomers of the claimed compounds (col. 2, line 45 - col. 3, line 37). A compound which is isomeric with a prior art compound is unpatentable absen[t] some unobvious or unexpected beneficial property not possessed by the prior art compound. In re Norris, 179 F.2d 970, 84 USPQ 458 (CCPA 1970)." (Office action, paragraph 8, lines 18-23). Applicants respectfully traverse this rejection.

In re Norris, 179 F.2d 970, 84 USPQ 458, 37 CCPA 876 (1950) concerns the patentability of the compound alpha, alpha-dimethyl-beta-amino-gamma-methyl-valero-nitrile, which is depicted by the Court as CH_3–$CH(CH_3)$–$C(=NH)$–$C(CH_3)_2$–$C\equiv N$. In holding this compound to be unpatentable over a prior art isomer, the Court relied, *inter alia*, on *In re Finley*, 174 F.2d 130, 81 USPQ 383, 36 CCPA 998 (1949) (affirming the unpatentability of 2-ethyl hexyl salicylate in view of the prior art compound normal octyl salicylate). The Court also took judicial notice of a chemistry textbook describing the predictability of the chemical properties of isomeric hydrocarbons. In reaching its decision, the Court quoted with approval a holding of *In re Hass*, 141 F.2d 127, 60 USPQ 548, 551, 31 CCPA 903 (1944) ("Whether novel chemical compounds are patentable over prior art isomers and homologues is a question to be determined in each case.").

Applicants respectfully submit that there are fundamental differences between the

compounds of the present invention (steroids) and simple hydrocarbons or nitriles and salicylates thereof. In particular, the chemical properties (*e.g.*, binding affinities) and biological activities of structural isomers of steroids do not vary regularly and predictably, as do the chemical and physical properties of simple hydrocarbons.

For example, it is known that the anesthetic steroids bind with $GABA_A$ receptors and have stringent structural requirements for biological activity. It is postulated that these requirements arise because the anesthetic steroids have two points of contact with $GABA_A$ receptors through two polar functional groups and that the hydrophobic portion of these molecules remain in contact with the fatty acyl chains of phospholipids surrounding $GABA_A$ receptors. Thus, structural isomers of the anaesthetic steroids may have profoundly different biological activities depending upon whether an isomeric unit enhances, does not affect or disrupts either a polar binding site or the hydrophobic backbone of the steroid. See, *e.g.*, Im, W.B., *et al.*, "Studies on the Mechanism of Interactions between Anesthetic Steroids and γ-Aminobutyric $Acid_A$ Receptors," *Molecular Pharmacology 37*:429-434 (1990) at page 433, column 2, last paragraph, line 26, through page 433, column 1, line 13 (IDS reference AS8). For discussions of experimentally determined differences in the anaesthetic effects of substitutions at the 2-, 3-, and 17-positions of steroids, see Phillips, G.H., "Structure-Activity Relationships in Steroidal Anaesthetics," *Journal of Steroid Biochemistry 6*: 607-613 (1975) (IDS reference AS12) and Phillips, G.H., "Structure-Activity Relationships in Steroidal Anaesthetics," *Molecular Mechanisms in General Anesthesia*, Halsey, M.J., *et al.* (Eds.), Glaxo Symposium, pp. 32-47 (1974) (IDS reference AT12).

Thus, the existence of a substitutent on a steroid does not provide one of ordinary skill in the art with any expectation of similar chemical properties or of significant biological activity

were a positional isomer of that steroid to be synthesized. Applicants respectfully submit that the Examiner's objection has been overcome and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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